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Glucocorticoid Inhibits Elevated Polyamine Biosynthesis in Psoriasis

DIANE H. RUSSELL, WENDELL L. COMBEST, ELIZABETH A. DUELL, MAREK A. STAWISKI, THOMAS F. ANDERSON, AND JOHN J. VOORHEES, M.D.

Department of Pharmacology, University of Arizona Health Sciences Center, Tucson, Arizona (DHR and WLC) and Departments of Dermatology (EAD, MAS, TFA and JJV) and Biological Chemistry (EAD), The University of Michigan Medical School, Ann Arbor, Michigan, U.S.A.

In the genetic skin disease psoriasis, the number of proliferating cells is 12-fold greater in lesional (involved) and 2.5-fold greater in uninvolved epidermis than in normal epidermis. Since increased polyamine biosynthesis is associated with cell proliferation, we measured polyamine levels and the activities of the polyamine biosynthetic enzymes from biopsies of involved and uninvolved psoriatic epidermis and normal epidermis. Polyamine (putrescine, spermidine, and spermine) levels were: (1) higher in involved than in uninvolved epidermis ($N = 7$, $P < 0.05$); (2) higher in uninvolved ($N = 7$) than in normal ($N = 8$) epidermis ($P < 0.02$); (3) higher in urine from psoriatic patients ($N = 7$) than in normal ($N = 8$) urine ($P < 0.02$). The activities of ornithine decarboxylase, and both putrescine and spermidine-stimulated S-adenosyl-L-methionine decarboxylase, were 6-fold higher in involved versus uninvolved ($N = 12$) or normal epidermis ($N = 12$, $P < 0.01$). After 24 hr of glucocorticoid pretreatment of lesions the activities of all 3 enzymes were markedly inhibited ($N = 12$, $P < 0.02$). Methylglyoxal bis (guanylhydrazone) and α-methylornithine inhibited the in vitro activities of S-adenosyl-L-methionine decarboxylase and ornithine decarboxylase, respectively, from lesional psoriatic epidermis. In conclusion: (1) the number of proliferating cells in the hyperproliferative epidermis of psoriasis and the increased polyamines are correlated; (2) glucocorticoid inhibits lesional polyamine biosynthetic enzyme activity and is known to clear psoriatic lesions; (3) non-glucocorticoid inhibitors of polyamine formation such as those given above might improve psoriatic lesions; (4) the discovery of elevated polyamine biosynthesis in both uninvolved and involved epidermis may lead to a better understanding of misregulated cell proliferation in this disease.

Psoriasis apparently is a multifactorial genetic skin disease which afflicts approximately 1–2% of the population of this country [1]. The psoriatic patient has scaly, elevated lesions (involved) which are separated by visually normal (uninvolved) areas of skin. In comparison with normal epidermis from volunteers, involved epidermis and uninvolved epidermis have a 12-fold [2] and 2.5-fold [3] increase, respectively, in the number of proliferating cells. Increased epidermal cell proliferation is a major and essential component of the pathophysiology of psoriasis [4].

The diamine, putrescine (Pu), and the polyamines, spermidine (Sp) and spermine (Sm), are known growth factors in bacterial and mammalian cell proliferation [5]. In fact, some investigators believe that polyamines are essential factors necessary for cell proliferation [6,7]. Since cell proliferation is central to the pathophysiology of psoriasis and since polyamines appear to be significant modulators of cell proliferation, our objective was to assess polyamine metabolism in normal and psoriatic epidermis. A schematic representation of the polyamine biosynthetic pathway is shown in Fig 1.

We report: (1) the levels of the polyamines Pu, Sp and Sm are significantly higher in involved and uninvolved psoriatic than in normal epidermis; (2) the activities of the polyamine biosynthetic enzymes ornithine decarboxylase (ODC) (EC 4.1.1.17, L-ornithine carboxy-lyase), putrescine-stimulated S-adenosyl-L-methionine decarboxylase (Pu-SAMD), and spermidine-stimulated S-adenosyl-L-methionine decarboxylase (Sp-SAMD) are significantly higher in involved than in uninvolved psoriatic epidermis.

MATERIALS AND METHODS

Selection of Subjects

Pu, Sp and Sm levels were measured in epidermal strips from 15 subjects (7 psoriatic patients and 8 normal volunteers). ODC, Pu-SAMD and Sp-SAMD activities were measured in epidermal strips from an additional 24 subjects (12 psoriatic patients and 12 normal volunteers). In psoriatic subjects, both diseased (visually involved) and visually normal (uninvolved) epidermis were analyzed. Psoriatic patients and volunteers were matched as closely as possible for sex and age. All subjects were 18 yr of age or older and were informed of the nature, purpose and potential risks of this study before their written, voluntary consent to participate was obtained. Pregnant women were excluded, as well as individuals using oral or topical medications for 1 week prior to the study.

Epidermal Biopsy

Epidermal strips were removed surgically using a modified variable-speed, motor-driven Castroviejo keratome as detailed previously [8]. Each strip was 1–2 cm wide and 1–4 cm long. The mean keratome shim setting for full-thickness lesional removal of involved epidermis was 0.350 mm. A shim setting of 0.125 mm was used to procure uninvolved and normal epidermal specimens. Involved, uninvolved and normal epidermal strips were removed after each area was cleansed with hexachlorophene and anesthetized by local infiltration of 1% lidocaine without epinephrine. The average time for the keratome to cut through uninvolved or normal and involved epidermis was 8 and 5 sec, respectively. Therefore, all epidermal strips were frozen in liquid nitrogen within less than 10 sec of removal from volunteers. A portion of

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Reprint requests to: John J. Voorhees, M.D., Department of Dermatology, University of Michigan Medical School, Ann Arbor, Michigan 48109.

Abbreviations:
ODC: ornithine decarboxylase
Pu: putrescine
Pu-SAMD: putrescine-stimulated S-adenosyl-L-methionine decarboxylase
Sm: spermine
Sp: spermidine
Sp-SAMD: spermidine-stimulated S-adenosyl-L-methionine decarboxylase

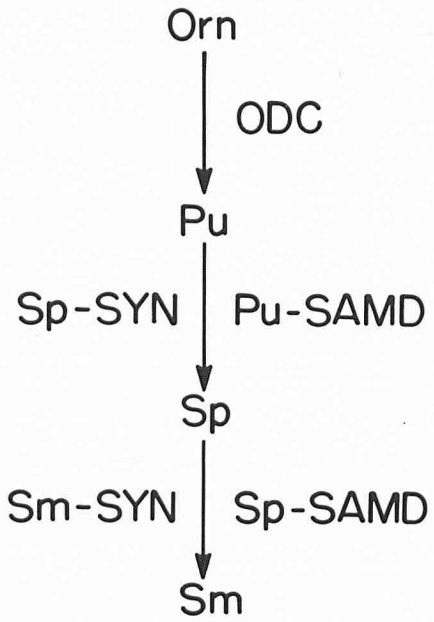

FIG 1. Schematic representation of the polyamine biosynthetic pathway. Abbreviations: *Orn*, ornithine; *Sp*-SYN, spermidine synthetase; *Sm*-SYN, spermine synthetase; other abbreviations in this and subsequent figures are in the introduction of the text. *Pu*, *Sp* and *Sm* as well as *ODC*, *Pu-SAMD* and *Sp-SAMD* were measured in epidermis taken from normal human volunteers and psoriatic (both visibly involved and uninvolved areas) patients.

involved, uninvolved and normal strips was processed for frozen section histology. Only strips containing full-thickness involved, uninvolved or normal epidermis and minimal dermal contamination as described [9] were analyzed.

Materials

[1-^{14}C] ornithine (5 mCi/mmol) and S-adenosyl-L-[carboxyl-^{14}C] methionine (7 mCi/mmol) were obtained from New England Nuclear, Boston, Massachusetts. Putrescine dihydrochloride, spermidine trihydrochloride, and spermine tetrahydrochloride were obtained from Sigma (St. Louis, Missouri) and recrystallized prior to use as standards. Dithiothreitol, EDTA and pyridoxal phosphate were obtained from Calbiochem, La Jolla, California. α-methylornithine (αMO) and methylglyoxal bis (guanylhydrazone) (MGBG) was a gift from Dr. Harry B. Wood of the National Cancer Institute.

Polyamine Measurements in Epidermis

Frozen epidermal strips from 8 normal volunteers and 7 psoriatic patients were pulverized with a mortar and pestle under liquid nitrogen and then sonicated for 1 min at 0–4°C with an ultrasonic cell disrupter equipped with an 11.2 cm probe (Electro-Mechanic Instrument Co., Perkasie, Pennsylvania) in 4 vol of 5% (W/V) trichloroacetic acid at 0–4°C. A sample of the supernatant was applied to the column of the Durrum D-500 amino acid analyzer (Palo Alto, California) for polyamine identification and quantitation. The details of this methodology have been described previously [10, 11].

Polyamine Measurements in Urine

From the 8 normal volunteers and 7 psoriatic patients who donated epidermal strips for polyamine analysis, we collected serum and 24 hr urine specimens. Polyamine levels were measured in urine as previously described [11] and the creatinine content of urine and serum was determined.

Design of Glucocorticoid Pretreatment Experiments

Twelve normal volunteers and 12 psoriatic patients participated in a double-blind evaluation of the effect of a potent new topical glucocorticoid, diflorasone diacetate, 0.05% on the activities of epidermal ODC, Pu-SAMD and Sp-SAMD. This concentration of diflorasone diacetate is known to clear psoriasis [12]. Twenty-four tube pairs, 1 tube containing glucocorticoid in cream vehicle and the other tube containing cream vehicle alone (control), were a gift from Dr. Carl Schlagel, The Upjohn Company, Kalamazoo, Michigan. Each tube pair was randomized and labeled, 1 tube with an A and the other with a B.

Six sites, 4 involved and 2 uninvolved were selected for treatment in psoriatic patients. These sites were labeled and randomized in such a way that cream from tube A was applied to 2 of the 4 involved and 1 of the 2 uninvolved sites. The 3 remaining sites, 2 involved and 1 uninvolved, received an application from tube B. Two sites were selected in the normal volunteers and randomly treated, 1 with cream from tube A and the other with cream from tube B. Each site in volunteers and psoriatic patients received one application which was placed under occlusive plastic film (Saran Wrap) and remained in place continuously for 24 hr. The area of each site was approximately 24 cm^2. Cross-contamination of the sites was avoided by both the plastic film dressing and by maintaining a distance of at least 6 inches between sites.

Twenty-four hours after application of the creams, the plastic film was removed, sites were gently cleansed and air-dried for 4 hr. Twenty-eight hours after application the epidermis from both normal sites in normal volunteers was removed surgically as described above. From the psoriatic patients epidermis from 4 sites, the 2 uninvolved sites and a random choice of 1 involved tube A treated and 1 involved tube B treated lesion, was removed. The remaining 2 involved sites were evaluated for clinical effects of treatments at 3 days, which is 2 days after applications were discontinued and which is also 2 days after the other sites were removed surgically. The identity of A and B in each tube pair was revealed after clinical observations and biochemical analyses were completed.

Preparation of Epidermis for Polyamine Biosynthetic Enzyme Analyses

The range of wet weights of epidermal strips was: 60–104 mg, normal; 30–96 mg, uninvolved; 82–348 mg, involved. Frozen epidermal strips were pulverized with a mortar and pestle under liquid nitrogen and hand homogenized 20 strokes in 5 vol of buffer containing 0.05 M sodium-potassium phosphate buffer (pH 7.2), 0.1 mM EDTA, 1.0 mM dithiothreitol, and 40 μM pyridoxal phosphate. Samples were homogenized in a 1-ml glass homogenizer (Radnotti Glass Co., Arcadia, California). The homogenate was transferred to a 1.5-ml polyethylene centrifuge tube (Sarstedt Laboratory Wares, Princeton, New Jersey) and centrifuged for 10 min at 17,300 ×g. The superantant solution was used as the source of polyamine biosynthetic enzymes.

Ornithine Decarboxylase Assay

Enzyme activity was determined by measuring the release of $^{14}CO_2$ from D,L-[1-^{14}C] ornithine as previously described [13, 14] with minor modifications. Reaction mixtures consisted of 50–100 μl of cell extract, 40 μM pyridoxal phosphate, 0.1 mM L-[1-^{14}C] ornithine and 80–130 μl of 0.5 M sodium-potassium phosphate buffer, pH 7.2 containing 1.0 mM dithiothreitol to make a total volume of 0.2 ml. After 30 min incubation at 37°C, the reaction was stopped by the addition of 0.2 ml 1 M citric acid. Enzyme activity was linear for 30 min and was proportional to the amount of epidermal supernatant added to the assay. Each sample was assayed in triplicate.

PU-SAMD and SP-SAMD Assays

Enzyme activity was determined by measuring the release of $^{14}CO_2$ from S-adenosyl-L-[carboxyl-^{14}C] methionine as previously described with minor modifications [15]. Reaction mixtures consisted of 50–100 μl of epidermal supernatant solution, 40 μM pyridoxal phosphate, either 2.5 mM putrescine dihydrochloride or 5 mM spermidine trihydrochloride, 0.15 mM S-adenosyl-L-[carboxyl-^{14}C] methionine, 70–120 μl of 0.05 M sodium-potassium phosphate buffer, pH 7.2 containing 1.0 mM dithiothreitol to make a final volume of 0.2 ml. Enzyme activity was linear for 30 min and was proportional to the amount of epidermal supernatant added to the assay. Each sample was assayed in duplicate.

Other Determinations

Epidermal protein and DNA content were determined by the methods of Lowry et al. [16] and Burton [17], respectively.

Data Analyses

Biochemical data were analyzed using a Student's *t*-test for paired and unpaired data with a one-sided hypothesis.

RESULTS

Polyamine Content of Uninvolved and Involved Epidermis from Psoriatic Patients is Increased in Comparison with that of Epidermis from Normal Subjects

Figure 2 shows that: (1) The mean Pu level in involved (0.14 ± 0.02 nmoles/μgm DNA) versus uninvolved (0.06 ± 0.01 nmoles/μgm DNA) is increased 133% ($P < 0.025$). Pu in uninvolved (0.06 ± 0.01 nmoles/μgm DNA) versus normal (0.03 ± 0.01 nmoles/μgm DNA) is increased 100% ($P < 0.025$); (2) Sp in involved (0.23 ± 0.02 nmoles/μgm DNA) versus uninvolved (0.07 ± 0.01 nmoles/μgm DNA) is increased 229% ($P < 0.001$). Sp in uninvolved (0.07 ± 0.01 nmoles/μgm DNA) versus normal (0.03 ± 0.01 nmoles/μgm DNA) is increased 133% ($P < 0.001$); (3) Sm in involved (0.10 ± 0.02 nmoles/μgm DNA) versus uninvolved (0.06 ± 0.01 nmoles/μgm DNA) is increased 67% ($P < 0.05$); Sm in uninvolved (0.06 ± 0.01 nmoles/μgm DNA) versus normal (0.03 ± 0.004) is increased 100% ($P < 0.005$).

Polyamine Content of Urine from Psoriatic Patients is Increased in Comparison with that of Urine from Normal Subjects

Figure 3 shows that: (1) The mean Pu content (2.3 ± 0.45 nmoles/mg creatinine) of urine from psoriatic patients in comparison with the Pu content (1.2 ± 0.15 nmoles/mg creatinine) of urine from normal subjects is increased 92% ($P < 0.02$); (2) the mean Sp content (1.8 ± 0.38 nmoles/mg creatinine) of urine from psoriatic patients versus the Sp content (0.75 ± 0.11 nmoles/mg creatinine) of urine from normal subjects is increased 140% ($P < 0.01$). Sm (data not shown) was present in trace amounts in both normal and psoriatic urine.

Ornithine Decarboxylase and S-Adenosyl-L-Methionine Decarboxylase Activities are Increased in Involved Versus Uninvolved Psoriatic Epidermis or Normal Epidermis From Volunteers

Figure 4 shows that: (1) The mean ODC activity in involved (79.6 ± 27.0 pmols $^{14}CO_2$/mg protein/30 min) versus uninvolved (10.3 ± 3.4 pmols $^{14}CO_2$/mg protein/30 min) is increased 673% ($P < 0.008$). Mean ODC activity in uninvolved (10.3 ± 3.4 pmols $^{14}CO_2$/mg protein/30 min) versus normal (6.1 ± 1.0 pmols $^{14}CO_2$/mg protein/30 min) showed a 69% increase which was not statistically significant ($P < 0.12$); (2) mean Pu-SAMD activity in involved (107.7 ± 24.9 pmols $^{14}CO_2$/mg protein/30 min) versus uninvolved (14.7 ± 2.8 pmols $^{14}CO_2$/mg protein/ 30 min) is increased 633% ($P < 0.002$). Mean Pu-SAMD activity in uninvolved and normal were similar; (3) mean Sp-SAMD activity in involved versus uninvolved was not performed due to insufficient quantity of psoriatic tissue. However, mean Sp-SAMD activity in involved (81.8 ± 12.9 pmols $^{14}CO_2$/mg protein/30 min) versus normal (11.1 ± 1.9 pmols $^{14}CO_2$/mg protein/ 30 min) was increased 637% ($P < 0.003$). In an experiment not shown in Fig 4, drugs were added to the enzyme assay mixtures. α-methylornithine (4.0×10^{-5} M) inhibited ODC activity from involved 50% whereas Pu-SAMD activity from involved was inhibited 50% by 0.6×10^{-6} M methylglyoxal bis (guanylhydrazone).

Ornithine Decarboxylase and S-Adenosyl-L-Methionine Decarboxylase Activities in Involved Psoriatic Epidermis are Decreased by In Vivo Glucocorticoid Pretreatment

Figure 4 shows that: (1) glucocorticoid reduced the ODC activity in involved from 79.6 ± 27.0 pmols $^{14}CO_2$/mg protein/30

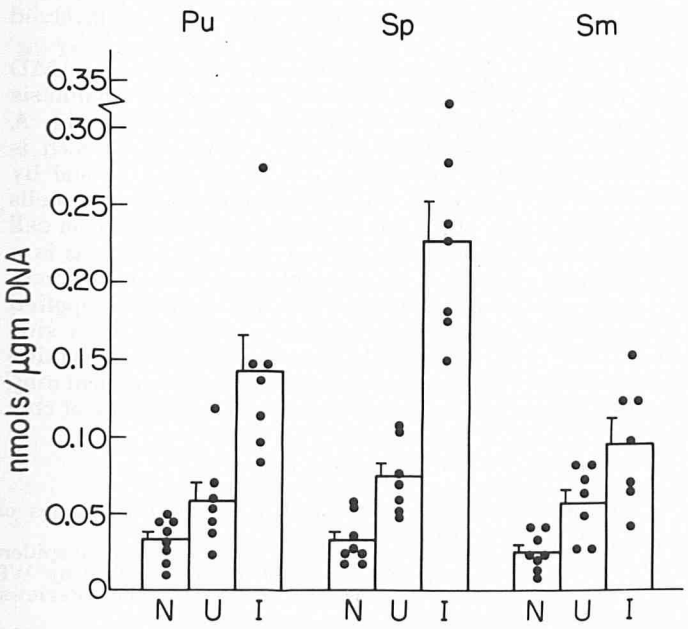

FIG 2. *Pu*, *Sp* and *Sm* levels (X̄ ± SEM) in normal human epidermis (N = 8) and in uninvolved and involved psoriatic epidermis (N = 7). In uninvolved versus normal epidermis and in involved versus uninvolved psoriatic epidermis, the mean level of all 3 polyamines was significantly increased. In Fig 2–4, each *black circle* is a data point for a single individual.

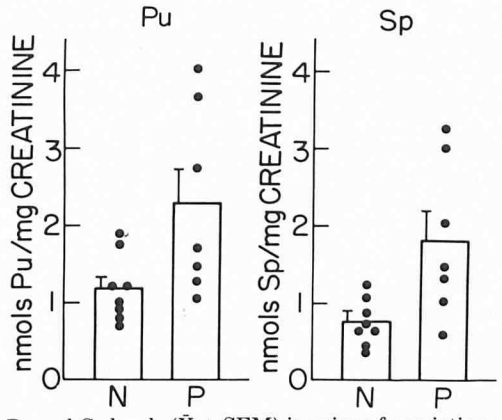

FIG 3. *Pu* and *Sp* levels (X̄ ± SEM) in urine of psoriatic patients (*P*) and of normal volunteers (*N*). Mean levels of *Pu* and *Sp* were significantly higher in psoriatic patients.

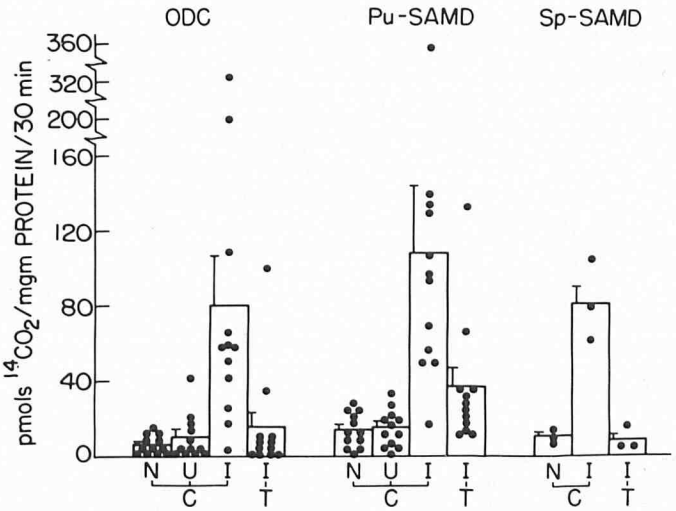

FIG 4. Activities (X̄ ± SEM) of the polyamine biosynthetic enzymes *ODC*, *Pu-SAMD*, and *Sp-SAMD* in control treated (N = 12) normal (*N-C*) epidermis, uninvolved (*U-C*) and involved (*I-C*) psoriatic (N = 12) epidermis, and in glucocorticoid treated involved (*I-T*) psoriatic epidermis.

min to 15.3 ± 8.2 pmols $^{14}CO_2$/mg protein/30 min, a decrease of 81% ($P < 0.025$); (2) glucocorticoid decreased mean Pu-SAMD activity in involved from 107.7 ± 24.9 pmols $^{14}CO_2$/mg protein/30 min to 35.9 ± 9.8 pmols $^{14}CO_2$/mg protein/30 min, a reduction of 67% ($P < 0.01$); (3) glucocorticoid reduced mean Sp-SAMD activity in involved from 81.8 ± 12.9 pmols $^{14}CO_2$/mg protein/30 min to 8.5 ± 3.8 pmols $^{14}Co_2$/mg protein/30 min, a decrease of 90% ($P < 0.01$).

DISCUSSION

The levels of Pu, Sp, and Sm as well as the activities of the 3 polyamine biosynthetic enzymes are significantly higher in involved epidermis than in uninvolved or normal (Fig 2 and 4). The elevated polyamine content parallels the increased number of proliferating cells reported in both involved and uninvolved epidermis of psoriasis [2, 3]. These data do not agree with a report by Proctor et al [18] of reduced Sp and Sm content in uninvolved epidermis from 2 psoriatic subjects.

Pu and Sp levels are higher in the urine of psoriatic patients than in the urine of normal subjects (Fig 3). We speculate that the elevations of the polyamines in the urine are perhaps derived from the involved and uninvolved epidermis. This is similar to elevated urinary polyamines in other pathologies such as cancer [19], where extracellular Pu levels reflect the growth fraction of the tumor and extracellular Sp reflects tumor cell loss [20]. Therefore, polyamine determinations are clinically useful to assess alterations in tumor kinetics in response to therapy [20]. Thus it might be possible to adjust systemic chemotherapy for psoriasis by monitoring polyamine levels in extracellular fluids.

Pu, Sp and Sm levels are significantly elevated in uninvolved versus normal epidermis, whereas ODC activity shows only a modest 69% increase ($P < 0.12$) in uninvolved versus normal where Pu-SAMD activity in uninvolved and normal are similar. The upward trend of ODC activity in uninvolved versus normal suggests that in a larger sample of subjects, the 3 polyamine biosynthetic enzyme activities might be significantly elevated in the hyperproliferative epidermis of uninvolved versus normal epidermis. Such an elevation of polyamine biosynthetic enzyme activity would be in accord with the elevated polyamine content of uninvolved versus normal epidermis reported here (Fig 2). The elevated arginase activity in involved epidermis reported by Rothberg and Van Scott [21] is also in accord with our data. The elevated arginase activity in psoriasis catalyzing ornithine formation may provide increased quantities of ornithine as substrate for the increased activity of the polyamine biosynthetic pathway.

Our finding of elevated Pu, Sp and Sm levels in involved versus uninvolved and in uninvolved versus normal as well as increased ODC, Pu-SAMD, and Sp-SAMD activities in involved versus uninvolved or normal is probably not specific for the hyperproliferative epidermis of psoriasis. For example, mechanical trauma such as wounding [22, 23] and mitogenic tumor promoters [24, 25] produce an initial induction of ODC activity followed by proliferation. It is well known that mechanical trauma to skin induces clinical lesions [26] in the individual genetically predisposed to psoriasis. Conversely, protein starvation markedly reduces ODC activity in traumatized rat skin [27], and starvation can improve or clear psoriasis [28]. Thus it is possible that stimulated polyamine biosynthesis is of importance in the pathophysiology of the proliferative compartment of involved and uninvolved epidermis.

In cultured HTC cells [29] and Reuber H35 cells [30] glucocorticoids and cyclic AMP stimulate ODC. Glucocorticoid inhibits epidermal proliferation [31] in psoriatic lesions, lesions have a reduced cyclic AMP/cyclic GMP ratio [32], and topical cyclic AMP elevating agents can improve lesions [33]. Thus our hypothesis was that glucocorticoid and cyclic AMP elevation would inhibit epidermal ODC activity, just the opposite of the action of these 2 effectors on ODC activity of other tissues. Although we have not yet studied the effect of cyclic AMP on the polyamine biosynthetic enzyme activities in involved epidermis, Fig 4 clearly shows that as predicted, glucocorticoid pretreatment of involved areas markedly inhibits ODC, Pu-SAMD and Sp-SAMD activities in comparison with lesional epidermis which had not been pretreated with glucocorticoid. This inhibition is not the nonspecific result of glucocorticoid clearing of psoriatic lesions because polyamine biosynthetic enzyme activities were measured after 28 hr glucocorticoid pretreatment. The pretreatment time was purposely insufficient to clear lesions so that at 3 days after pretreatment the degree of thickness in the non-surgically removed glucocorticoid treated lesions was similar to that observed at the time of initial lesional evaluation as detailed elsewhere [9]. Thus it is probable that the marked reduction in polyamine biosynthetic enzyme activities is the result of glucocorticoid induced reversible early molecular events.

The inhibition of polyamine biosynthetic enzymes in lesional epidermis by glucocorticoid pretreatment is consistent with work which demonstrates inhibition of wound induced stimulation of ODC activity in epidermis of rats by glucocorticoid [22]. In that study [22] glucocorticoid delayed the expression of enzyme activity, thus producing an apparent rather than an actual inhibition of enzyme activity. In our study glucocorticoid may be acting similarly, producing an apparent inhibition of enzyme activity. The data in this paper are limited and show that at one time point, 28 hr, glucocorticoid produces an apparent reduction in polyamine biosynthetic enzyme activity. A future study using several time points in psoriasis will be required to obtain a complete assessment of steroid effects on this enzyme system.

During the cell cycle, ODC is induced specifically during the late G_1 phase in synchronized Chinese hamster lung fibroblasts [34]. If glucocorticoid inhibits or stimulates the cell cycle in the G_2, M or early G_1 phase of the cell cycle, ODC activity would decrease or increase due to an effect on cell cycle progression rather than a direct effect on ODC. Since glucocorticoids block epidermal cells in the G_1 and G_2 phase of the cell cycle [35], it is not clear whether inhibition of ODC activity by glucocorticoid pretreatment (Fig 4) is a cell cycle specific block, or whether it results from a more direct inhibition of ODC activity in involved epidermis.

α MO and MGBG are known inhibitors of ODC and SAMD [5–7]. MGBG inhibits spermidine formation and DNA synthesis in lymphocytes stimulated to proliferate by concanavalin A [6]. In cultured hepatoma cells α MO inhibits ODC which is followed by a fall in the cellular levels of Pu and Sp and by reduced cell proliferation. In these cultured hepatoma cells exogenous addition of Pu and Sp results in a resumption of cell proliferation [7]. If inhibition of polyamine biosynthesis is a significant component of the antiproliferative action of glucocorticoids in psoriasis, agents such as α MO and MGBG applied topically might improve the psoriatic lesion with fewer side effects than glucocorticoids. In any case, elevated polyamine biosynthesis in the entire epidermis of the psoriatic patient may lead to a better understanding of the pathophysiology of this disease.

REFERENCES

1. Watson W, Cann HM, Farber EM, Nall LM: The genetics of psoriasis. Arch Dermatol 105:197–207, 1972
2. Weinstein GD, McCullough JL: Cytokinetics in diseases of epidermal hyperplasia, Annual Review of Medicine. Edited by WP Creger, CH Coggins, EW Hancock. Palo Alto, Annual Reviews, 1973, vol 24 pp 345–351
3. Goodwin P, Hamilton S, Fry L: A comparison between DNA synthesis and mitosis in uninvolved and involved psoriatic epidermis and normal epidermis. Br J Dermatol 89:613–617, 1973
4. Van Scott EJ: Tissue compartments of the skin lesion of psoriasis. J Invest Dermatol 59:4–6, 1972
5. Russell DH: the roles of polyamines, putrescine, spermidine and spermine in normal and malignant tissues. Life Sci 13:1635–1647, 1973

6. Fillingame RH, Jorstad CM, Morris DR: Increased cellular levels of spermidine or spermine are required for optimal DNA synthesis in lymphocytes activated by concanavalin A. Proc Natl Acad Sci USA 72:4042–4045, 1975
7. Mamont PS, Böhlen P, McCann PP, Bey P, Schuber R, Tardif C: α-Methyl ornithine, a potent competitive inhibitor of ornithine decarboxylase, blocks proliferation of rat hepatoma cells in culture. Proc Natl Acad Sci USA 73:1626–1630, 1976
8. Hammarström S, Hamberg M, Samuelsson B, Duell EA, Stawiski MA, Voorhees JJ: Increased concentrations of nonesterified arachidonic acid, 12L-hydroxy-5,8,10,14-eicosatetraenoic acid, prostaglandin E_2, and prostaglandin $F_{2\alpha}$ in epidermis of psoriasis. Proc Natl Acad Sci USA 72:5130–5134, 1975
9. Hammarström S, Hamberg M, Duell EA, Stawiski MA, Anderson TF, Voorhees JJ: Glucocorticoid in inflammatory proliferative skin disease reduces arachidonic and hydroxyeicosatetraenoic acids. Science 197:994–996, 1977
10. Marton LF, Vaughn JG, Hawk IA, Levy CC, Russell DH: Elevated polyamine levels in serum and urine of cancer patients: Detection by a rapid automated technique utilizing an amino acid analyzer, Polyamines in Normal and Neopalstic Growth. Edited by DH Russell. New York, Raven Press, 1973 pp 367–372
11. Russell DH, Russell SD: Relative usefulness of measuring polyamines in serum, plasma, and urine as biochemical markers of cancer. Clin Chem 21:860–863, 1975
12. Bluefarb SM, Howard FM, Leibsohn E, Schlagel CA, Wexler L: Diflorasone diacetate: Vasoconstrictor activity and clinical efficacy of a new topical corticosteroid. J Int Med Res 4:454–461, 1976
13. Russell DH, Snyder SH: Amine synthesis in rapidly growing tissues: Ornithine decarboxylase activity in regenerating rat liver, chick embryo and various tumors. Proc Natl Acad Sci USA 60:1420–1427, 1968
14. Russell DH, Snyder SH: Amine synthesis in regenerating rat liver: Effect of hypophysectomy and growth hormone on ornithine decarboxylase. Endocrinology 84:223–228, 1969
15. Pegg AE, Williams-Ashman HG: On the role of S-adenosyl-L-methionine in the biosynthesis of spermidine by rat prostate. J Biol Chem 244:682–693, 1969
16. Lowry OH, Rosebrough MJ, Farr AL, Randall RJ: Protein measurement with the folin phenol reagent. J Biol Chem 193:265–275, 1951
17. Burton K: Determination of DNA concentration with diphenylamine, Methods in Enzymology. Edited by L Grossman, K Moldave. New York, Academic Press, 1968, vol 12 part B, pp 163–166
18. Proctor MS, Fletcher Jr. HV, Shukla J, Rennert OM: Elevated spermidine and spermine levels in the blood of psoriasis patients. J Invest Dermatol 65:409–411, 1975
19. Russell DH: Increased polyamine concentrations in the urine of human cancer patients. Nature 233:144–145, 1971
20. Durie BGM, Salmon SE, Russell DH: Polyamines as markers of response and disease activity in cancer chemotherapy. Cancer Res 37:214–221, 1977
21. Rothberg S, Van Scott E: Evaluation of arginase activity in normal epidermal tissue and pathological stratum corneum. J Invest Dermatol 31:263–268, 1958
22. Mizutani A, Inoue H, Takeda Y: Changes in polyamine metabolism during wound healing in rat skin. Biochim Biophys Acta 338:183–190, 1974
23. Probst E, Krebs A: Ornithine decarboxylase activity in relation to DNA synthesis in mouse interfollicular epidermis and hair follicles. Biochim Biophys Acta 407:147–157, 1975
24. O'Brien TG, Simsiman RC, Boutwell RK: Induction of the polyamine biosynthetic enzymes in mouse epidermis and their specificity for tumor promotion. Cancer Res 35:2426–2433, 1975
25. Yuspa SH, Lichti U, Ben T, Patterson E, Hennings H, Slaga TJ, Colburn N, Kelsey W: Phorbol esters stimulate DNA synthesis and ornithine decarboxylase activity in mouse epidermal cell cultures. Nature 262:402–404, 1976
26. Baker H: Psoriasis: a review. Dermatologica 150:16–25, 1975
27. Morrison D, Goldsmith LA: Ornithine decarboxylase in rat skin. in press, J Invest Dermatol vol 70, June 1978
28. Simons RDG: Additional studies on psoriasis in the tropics and in starvation camps. J Invest Dermatol 12:285–294, 1949
29. Canellakis ZN, Theoharides TC: Stimulation of ornithine decarboxylase synthesis and its control by polyamines in regenerating rat liver and cultured rat hepatoma cells. J Biol Chem 251:4436–4441, 1976
30. Byus CV, Wicks WD, Russell DH: Induction of ornithine decarboxylase in Reuber H35 rat hepatoma cells. J Cyclic Nucleotide Res 2:241–250, 1976
31. Goodwin P, Fry L: The effects of corticosteroids and methotrexate on DNA synthesis in psoriasis, Mechanisms of Topical Corticosteroid Activity. Edited by LC Wilson, R Marks. New York, Churchill Livingstone 1976, chap 6, pp 47–53
32. Voorhees JJ, Colburn NH, Stawiski M, Duell EA, Haddox M, Goldberg ND: Imbalanced cyclic AMP and cyclic GMP levels in the rapidly dividing, incompeltely differentiated epidermis of psoriasis, Control of Proliferation in Animal Cells. Edited by B Clarkson, R Baserga, New York, Cold Spring Harbor Laboratory, 1974, pp 635–648
33. Voorhees JJ, Duell EA, Stawiski M, Harrell ER: Cyclic nucleotide metabolism in normal and proliferating epidermis, Advances in Cyclic Nucleotide Research. Edited by P Greengard, GA Robison. New York, Raven Press, 1974, vol 4, pp 117–162.
34. Russell DH, Stambrook PJ: Cell cycle specific fluctuations in adenosine 3′:5′-cyclic monophosphate and polyamines of chinese hamster cells. Proc Natl Acad Sci USA 72:1482–1486, 1975
35. Marks R, Williams K: The action of topical corticosteroids on the epidermal cell cycle, Mechanisms of Topical Corticosteroid Activity. Edited by LC Wilson, R Marks. New York, Churchill Livingstone, 1976, chap 4, pp 39–46

United Scleroderma Foundation Award

The United Scleroderma Foundation plans to award $3000 for the best original scleroderma research paper published in 1978.

Recipients of this award in 1979 were Drs. Hirabumi Kondo, Bruce Rabin, and Gerald P. Rodnan who received $1000 for their paper "Cutaneous Antigen-Stimulating Lymphokine Production by Lymphocytes of Patients with Progressive Systemic Sclerosis" (*J. Clin Inv* 58:1388–1399, 1976).

The award is designed for the individual or group whose investigative work in this field has been outstanding. Names of applicants for the award, together with supporting data, should be submitted for consideration by December 1, 1978. Results of the research must have been presented at a scientific medical meeting or published in a recognized medical journal. The award recipient will be determined by a committee.

Address all communications to Denny L. Tuffanelli, MD, Department of Dermatology, University of California, School of Medicine, San Francisco, CA 94143.